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The use of 4-Demethyl-4-Cholesteryloxyphenclomedine [DM-CHOC-PEN] as Therapy in Adolescent and Young Adult (AYA) Subjects with Advanced Malignancies Involving the Central Nervous System (CNS)

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Introduction- In 2020 about 89,000 adolescents and young adults (AYA) (ages 15 to 39) were estimated to be diagnosed with cancer in the United States, 23,890 had CNS and spinal nervous system (SNS) involvement—accounting for one twentieth or five percent of the number cancer diagnoses in the United States. The estimated deaths for this group was 18,020 deaths in 2020 (1).

This, is about eight times the number of cancers diagnosed in children ages 0 to 14 (2).

The National Cancer Institute (NCI) and the American Cancer Society (ACS), in conjunction with the World Health Organization (WHO), EORTC, ECCO, and UK Cancer Foundation estimate that nearly 15% of CNS and SNS tumors worldwide involve the adolescent/ young adult (AYA) age group (3, 4).

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The use of 4-Demethyl-4-Cholesteryloxypenclomedine [DM-CHOC-PEN] as Therapy in Adolescent and Young Adult (AYA) Subjects with Advanced Malignancies Involving the Central Nervous System (CNS)

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INTRODUCTION

In 2020 about 89,000 adolescents and young adults (AYA) (ages 15 to 39) were estimated to be diagnosed with cancer in the United States, 23,890 had CNS and spinal nervous system (SNS) involvement—accounting for one twentieth or five percent of the number cancer diagnoses in the United States. The estimated deaths for this group was 18,020 deaths in 2020 (1).

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The National Cancer Institute (NCI) and the American Cancer Society (ACS), in conjunction with the World Health Organization (WHO), EORTC, ECCO, and UK Cancer Foundation estimate that nearly 15% of CNS and SNS tumors worldwide involve the adolescent/young adult (AYA) age group (3, 4).

The most common types of cancer involving the CNS and SNS diagnosed in the AYA population are primary brain tumors (glioblastoma (GBM), astrocytoma, etc.) and metastatic cancers – *melanoma, leukemia, and sarcoma* (2, 3, 5).

For both male and female individuals <20 years of age, primary and secondary cancers of the CNS and SNS are the most common causes of death from cancer. In the 20-39 year age group, CNS/SNS cancers are the first cause of cancer-related deaths in males and the fifth cause of cancer-related deaths in females (2). Overall, in the 15 - 39-year old range – 5-year survivals have remained stagnant since 1995. However, for individuals aged 30 to 34, survival rates have decreased (2). The incidence and histology of cancer types do vary according to subject age and gender (2, 3).

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Results from surgery and radiation for localized non-invasive cancers are encouraging for all ages, including AYAs. However, for advanced disease, unless a tumor possesses a phenotypic target or a genetic mutation, the long term outlook for survival beyond one year are limited (4). Yes, the standard of care—chemotherapy, and radiation provide responses with improved survival; however, the long-range prognosis is still not 100% (4). Unfortunately, AYA aged individuals with advanced CNS involvement do not have a good prognosis (5).

The AYA aged group of individuals with malignancies deserves special attention since they generally lack histories of comorbidities. This age group are still at risk for toxicity with immune chemotherapy regimens in current use. AYA individuals with cancer also demonstrate different host biology, tumor pathophysiology (2, 4). They metabolize chemotherapy drugs differently than do either younger or older individuals (2, 4). Unfortunately, there are few AYA oncology specialists available (6).

Weiner *et al* presented early Phase I results and experiences with 4-demethyl-4-cholesteryl-oxyphenclomedine (DM-CHOC-PEN) as a treatment for AYA individuals with cancers involving the CNS (6). Encouraging responses are reported for the use of DM-CHOC-PEN in AYA subjects in *Table 1* without Gr-3/4 toxicities. The Phase II clinical trials with DM-CHOC-PEN continue (6, 8).

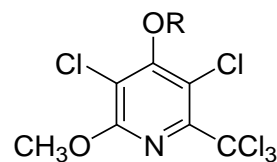


Fig. 1: Penclomedine analogs – PEN (R=CH₃); DM-PEN (R=H); DM-CHOC-PEN (R= CO₂-cholesteryl)

Table 1 reviews the AYA subjects treated to date with intravenous doses (39, 55, or 97.8 mg/m² of DM-CHOC-PEN administered once every 21 days), along with their responses and toxicities. To date, nineteen (19) subjects in the AYA age group with advanced, chemo-resistant stage IV cancer- melanoma, NSCLC, breast, acute lymphocytic leukemia, oligodendroglioma, or astrocytoma have been enrolled and treated (7, 8).

Unlike patients treated with other penclomedines (PEN, NSC 338720, Fig.1), DM-CHOC-PEN is non-neurotoxic (7). DM-CHOC-PEN crosses the blood-brain barrier (BBB) with responses observed in AYA subjects with sarcoma, astrocytoma, melanoma, ALL, lung, and breast cancers involving the spinal and central nervous systems- Table 1. The drug has been identified and measured in human sarcoma and lung cancer tissues (in concentrations of 61-120 ng/g of tumor

tissue) involving the CNS and not detected in adjacent normal brain tissue (7, 8).

DM-CHOC-PEN does not require hepatic activation and is active *invitro* in nanogram quantities- melanoma GBM, non-small cell lung cancer (NSCLC), and breast cancer explants (7, 8). The drug does not require hepatic activation, which is in contrast to other penclomedines - DM-PEN (Fig. 1) and other analogs (7). These observations have led to a proposed mechanism whereby DM-CHOC-PEN associates with erythrocyte membrane surfaces, penetrates the BBB and brain parenchyma and transported into intracerebral tumors with L-glutamine, with which it shares common structural moieties (7). Thus, DM-CHOC-PEN may be multifunctional - killing micro-metastases, inhibiting DNA repair and inducing an 'abscopal' immune-type effect (7, 8). The latter mechanism of action continues to be supported (9).

Table 1: AYA Subjects with Advanced Cancers Treated with IV DM-CHOC-PEN⁺⁺

Cancer Type (#)	Age/Sex	Dose (mg/m ²)	Responders w/ CNS (#)	OS (w/CNS) (mos)	Toxicity	
Breast (4)	33/F	29/F	50	1	12	None
	32/F		50	0	3	None
	30/F		39	0	4	None
			98	0	3	None
Pontine glioma (1)	22/M		50	NR	4	None
Melanoma (1)	39/F		75***	0	3	None
Gastric (1)	19/F		75***	NR	3	None
GBM (4)	36/M		50	NR	5	None
	34/F		75	NR	4	Nausea (Gr-2)
	34/F		98.7	NR	2	None
	24/F		75	Stable	3	None
	24/M		75	Too soon	3	None
ALL (1) NHL (1)	39/M		98.7	CR	8**	None
	28/F*		98.7	No response	6	None
Oligoastrocytoma (1)	39/M	34/F	98.7	NR	3	None
Oligodendroglioma (1)			85.8	NR	4	None
Astrocytoma (1)	31/M		98.7	1	59	None
Lung cancer (NSCLC) (1)	39/F		98.7	1	69+	Vasogenic edema (Gr-2)
H & N (1)	32 (M)		98.7	NR	6	None
Melanoma (1)	34 (F)		98.7	NR	3	None

*No CNS disease & no responses; **CNS – CR, w/peripheral progression; ***Liver disease (malignant or chronic)

**DM-CHOC-PEN was administered IV once every 21-days; *No CNS disease – no responses; **CNS – CR, w/ peripheral progression

The pharmacokinetic profile for DM-CHOC-PEN in the AYA subjects with a lower T_{1/2β} – 28:71 h reflects a 'healthier' metabolic profile for the drug compared with older adults, who may have been receiving medications for associated comorbidities resulting in induced hepatic metabolic activity (9).

Moreover, AYA subjects– 15-39 years old – are of major interest since they are not commonly enrolled in clinical trials and typically managed by pediatric and adult oncologists, rather than AYA oncology specialists who also appreciates the physical, psychosocial, emotional, sexual, spiritual, financial, dietary, etc.

peculiarities of this age group and, therefore apply specialized knowledge to their care (10, 11).

A Phase II clinical trial with DM-CHOC-PEN in AYA subjects (15-39 years old) with malignancies involving the CNS is in progress to validate and expand the observations in *Table 1* [IND 68,876] (12).

A blog is now available to follow the clinical trial's progress and information generated for the AYA population (12).

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